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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/229,173	01/13/1999	DEB K. CHATTERJEE	0942.2800008	7438

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/229,173	CHATTERJEE, DEB K.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment of claims 43 and 44 and the cancellation of claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29, and 34-37, in the paper of 10/08/2004, is acknowledged. Claims 38-44 are still at issue and are present for examination.

Applicants' arguments filed on 9/20/2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claim 40 is objected to because of the following informalities:

Claim 40 lists an amino acid sequence, which should have a sequence identifier following the sequence.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 is rejected under this statue as being indefinite in that it is unclear with respect to two different issues. First, claim 41 recites "the *Tma* DNA polymerase of claim 40", wherein claim 40 is drawn to "A mutant Tma DNA polymerase", not a "Tma

DNA polymerase". Thus there is no antecedent basis for the recitation "the Tma DNA polymerase of claim 40". Second, the recitation of "wherein said mutation is a $Phe^{730} \rightarrow Tyr^{730}$ substitution" is somewhat unclear in that "Phe^{730}" is unclear absent a reference sequence. For the purpose of advancing prosecution, claim 41 is interpreted as being directed to "the mutant *Tma* DNA polymerase of claim 40" and the reference to "Phe^{730}" is interpreted as corresponding to a substitution in that "Phe residue in the RXXXKXXXFXXXYX sequence".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 38 and 40-44 are directed to all possible "mutant *Tma* DNA polymerases having a mutation in the O-helix resulting in said DNA polymerase becoming non-discriminating against dideoxynucleotides or fragments of said mutant DNA polymerases having polymerase activity. The genus of "mutant DNA polymerases encompassed by "mutant *Tma* DNA polymerases" is interpreted as any polypeptide having polymerase activity, by virtue of the recitation of "mutant". The specification, however, only provides the representative species of 'mutant *Tma* DNA polymerases"

encompassed by these claims as those Tma Pol-I type DNA polymerases in which the polymerase consists of a mutation in the O-helix defined by RXXXKXXXFXXXYX (SEQ ID NO: 1). There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these "mutant Tma DNA polymerases" by any identifying structural characteristics or properties other than the activities recited in claims 38, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 38 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Tma DNA polymerase having the amino acid sequence of SEQ ID NO: 3, which is mutated in the O-helix as defined by RXXXKXXXFXXXYX, does not reasonably provide enablement for any mutant *Tma* DNA polymerases having a mutation in the O-helix resulting in said DNA polymerase becoming non-discriminating against dideoxynucleotides or fragments of said mutant DNA polymerases having polymerase activity. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 38 and 40-44 are so broad as to encompass any mutant *Tma* DNA polymerases having a mutation in the O-helix resulting in said DNA polymerase becoming non-discriminating against dideoxynucleotides or fragments of said mutant DNA polymerases having polymerase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polymerases broadly encompassed by the claims, including any polymerase and variant thereof maintaining polymerase activity. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed "mutant polymerases" and methods of their use. As discussed both above, under written description and below, under the art rejections, those polymerases encompassed by "mutant *Tma* DNA polymerases" are interpreted as any DNA polymerase and variant thereof, by virtue of the descriptor "mutant" and applicants have not limited the extent of those mutants encompassed by this term beyond the

maintenance of polymerization activity. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those Tma DNA polymerase having the amino acid sequence of SEQ ID NO: 3, which is mutated in the O-helix as defined by RXXXKXXXFXXXYX.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant DNA polymerase because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase activity; (B) the general tolerance of polymerases to modification and extent of such tolerance; (C) a rational and predictable

scheme for modifying any amino acid residue of a polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the polymerase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed polymerase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutant DNA polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 38, 40-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Tabor et al. (U.S. Patent No. 5,614,365, See IDS).

Tabor et al. teach a number of mutant DNA polymerases having a modified DNA binding site and their use in DNA sequencing reactions. Specifically, Tabor et al. teach a number of "mutant DNA polymerases having a mutation in the O-helix resulting in said DNA polymerase becoming non-discriminating against dideoxynucleotides" and the use of such DNA polymerases in methods of synthesizing, amplifying and sequencing DNA. While Tabor et al. does not teach such "mutant DNA polymerases" in which the corresponding wild-type polymerase enzyme is isolated from *Thermotoga maritima*, the

mutant DNA polymerases taught by Tabor et al. are considered to anticipate the claimed "mutant Tma DNA polymerase" by virtue that a "mutant Tma DNA polymerase" encompasses all DNA polymerases, by virtue of the descriptor "mutant". That is the only necessary characteristic of a "mutant Tma DNA polymerase" is that the polypeptide have polymerase activity. There are no structural characteristics associated with a "mutant" or with a "mutant Tma DNA polymerase".

Thus Tabor et al. anticipates claims 38 and 40-44.

Claims 38 and 40-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnes (Gene, Vol 112, pp 29-35, 1992, See IDS).

Barnes teaches a "fragment of a mutant Tma DNA polymerase". Specifically, Barnes teach a N-terminally truncated Thermus aquaticus (*Taq*) DNA polymerase. As discussed above in the rejection over Tabor et al., while Barnes does not teach such "mutant DNA polymerases" in which the corresponding wild-type polymerase enzyme is isolated from *Thermotoga maritima*, the mutant DNA polymerases taught by Barnes is considered to anticipate the claim to "a fragment of said mutant DNA polymerase said fragment having polymerase activity" by virtue that a "mutant *Tma* DNA polymerase" encompasses all DNA polymerases, by virtue of the descriptor "mutant". That is the only necessary characteristic of a "mutant *Tma* DNA polymerase" is that the polypeptide have polymerase activity. There is no structural characteristics associated with a "mutant" or with a "mutant *Tma* DNA polymerase" and as such the fragment taught by Barnes et al. anticipates claims 38 and 40-44.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

rgh
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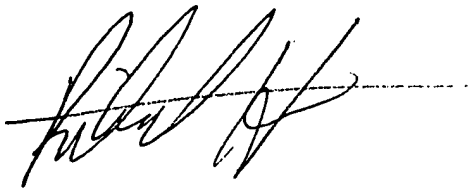

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